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CLINICAL INVESTIGATIONS

Predictors and long-term outcome of super-responders to cardiac resynchronization therapy

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Background: The level of improvement in left ventricular ejection fraction (LVEF) in super-responders to cardiac resynchronization therapy (CRT) is exceptional. However, the long-term prognosis remains unknown in a large population.

Hypothesis: Whether super-responders haven good long-term outcomes.

Methods: We registered 347 patients with primary CRT-D indication. Super-response was defined by LVEF >50% at follow-up echocardiogram. Best-subset regression analysis identified predictors of super-response. Endpoints were major adverse cardiac events (MACE; eg, all-cause mortality or heart failure hospitalization, cardiac death, and appropriate ICD therapy).

Results: Fifty-six (16%) patients with LVEF >50% were classified as super-responders. Female sex (OR: 3.06, 95% CI: 1.54-6.05), nonischemic etiology (OR: 2.70, 95% CI: 1.29-5.68), higher LVEF at baseline (OR: 1.07, 95% CI: 1.02-1.13), and wider QRS duration (OR: 1.17, 95% CI: 1.04-1.32) were predictors of super-response. Cumulative incidence of MACE at a median of 5.3 years was 18% in super-responders, 22% in responders, and 51% in nonresponders ($P < 0.001$). None of super responders died from cardiac death, compared to 9% of responders and 25% of non-responders ($P < 0.001$). None of super-responders experienced appropriate ICD therapy, compared with 10% of responders and 21% of non-responders ($P < 0.001$). In super-responders, the adjusted hazard ratio was 0.37 (95% CI: 0.19-0.73) for MACE and 0.44 (95% CI: 0.20-0.95) for total mortality, compared with non-responders.

Conclusions: Female sex, non-ischemic etiology, higher baseline LVEF, and wider QRS duration were independently associated with super-response. Super-response was associated with persistent excellent prognosis regarding survival and appropriate ICD therapy during long-term follow-up.

KEYWORDS

super-response, cardiac resynchronization therapy, long term prognosis and predictors

1 | INTRODUCTION

Several large clinical trials have demonstrated that cardiac resynchronization therapy (CRT) reduces symptoms, mortality, and heart failure (HF) hospitalization and improves cardiac function in the majority of patients with symptomatic HF and reduced left ventricular ejection fraction (LVEF; ≤35%) with wide QRS (>120 ms).[1–3] There is, however, wide variability in the extent of left ventricular (LV) remodeling and improvement in LVEF with CRT. Recent studies have indicated that in certain patients, "super-responders," there is an exceptional improvement of LV function after CRT, leading to an apparent marked recovery with LVEF >50%. This improvement in LVEF is associated with reduced HF deaths, implantable cardioverter-defibrillator (ICD) shocks, and hospitalizations,[4–6] and previous studies demonstrated an excellent long-term prognosis of super-responders.[7–12] However, these studies used different definitions for super-responders and reported different survival and ICD-intervention rates. Furthermore, most studies had a relative short

follow-up period and did not assess independent predictors of super-response. Therefore, the aims of our study were to identify patient characteristics associated with super-response to CRT and to evaluate the long-term all-cause and cardiac death, hospitalization due to worsening HF, and appropriate defibrillator intervention rate in patients with super-response, in a large cohort.

2 | METHODS

2.1 | Patient selection

From January 2004 to December 2009, four-hundred thirty-three consecutive patients with primary indication for cardiac resynchronization therapy defibrillator (CRT-D) implantation were included in the registry and followed for a median of 5.5 years (interquartile range [IQR], 4.5–6.5 years). This registry was approved by the institutional review board. Patients with cardiac resynchronization therapy pacemaker (CRT-P), LVEF ≥35% at the baseline, and recent myocardial infarction or coronary artery bypass grafting (<3 months) were excluded. To be included in the final analysis, the patients were required to have an echocardiogram before CRT-D implantation and during follow-up (see Supporting Information, Figure, in the online version of this article). LVEF assessment was made in all baseline and follow-up examinations (mean echocardiographic follow-up, 2.3 years [IQR, 1.4–3.9 years]). Patients were divided into 3 groups based on LVEF at follow-up echocardiogram. Patients with LVEF >50% were labeled super-responders (n = 56); those with LVEF of 30% to 50% were labeled responders (n = 153); and those with LVEF <30% were labeled nonresponders (n = 138).[8] Indication for CRT-D implantation was determined according to the guidelines at the time of implantation. In all patients, LVEF was ≤35% and QRS duration was >120 ms. Etiology was considered ischemic in the presence of significant coronary artery disease (≥50% stenosis in ≥1 major epicardial coronary artery) and/or history of myocardial infarction or prior revascularization by percutaneous coronary intervention or coronary artery bypass grafting. Medical therapy was optimized to reach the highest tolerated dosages of angiotensin-converting enzyme inhibitors and β-blockers.

2.2 | Device implantation

CRT devices from all major manufacturers (Medtronic, St. Jude Medical, Boston Scientific, Biotronik, and Sorin Group) were implanted. The majority of coronary sinus leads were bipolar and were positioned in the lateral, posterolateral, or posterior region when feasible (83%). The anterior and anterolateral positions were considered suboptimal and were avoided if possible (8%). Nine percent of coronary sinus leads were positioned epicardially, mostly during open heart surgery prior to CRT-D implantation. After implantation, tailored device programming was performed before discharge with 3 consecutive zones in the large majority of patients: (1) the ventricular tachycardia (VT) monitoring zone between 170 and 200 bpm; (2) the VT zone with anti-tachycardia pacing (ATP) and shock therapy between 200 and 230 bpm; and (3) the ventricular fibrillation (VF) zone with ICD shock >230 bpm. In ATP and shock therapy zone, arrhythmias were initially attempted to be terminated by 2 bursts and 1 ramp, and defibrillator shocks were used if the ventricular arrhythmia continued.

2.3 | Follow-up

Baseline patient characteristics data were collected prospectively and analyzed retrospectively. Routine follow-up visits were scheduled at 2 months post-implantation and every 6 months thereafter. As part of routine clinical care, during follow-up, ICD printouts were checked, ICD treatments were registered, and intracardiac electrograms were classified by device-cardiologist. Appropriate ICD therapy (ATP and shocks) was defined as ICD therapy delivered in response to sustained VT or VF. The routine follow-up in some of patients took place in referring hospitals. The clinical status of all survivals at the closure of the study (December 2013) was verified. The echocardiogram performed between 6 and 18 months after the implantation was used to determine the LVEF response to CRT. The echocardiography images were obtained on a Vivid 7 ultrasound machine (General Electric, Milwaukee, Wisconsin) using a 3.5-MHz transducer at a depth of 16 cm in the parasternal (long- and short-axis) and apical (2- and 4-chamber) views. The images were stored in cine-loop format by well-trained echocardiographers and reviewed by an independent cardiologist who was not involved in the study. The left ventricular end-diastolic diameter, left ventricular end-diastolic volume, left ventricular end-systolic diameter, and left ventricular end-systolic volume were measured, if possible, and the LVEF was calculated using the Simpson technique.[13]

2.4 | Event subclassification and definitions

Data on mortality were collected from reviewing hospital records, referring hospitals, and by contacting general practitioners. Causes of death were categorized into 2 groups, cardiac death and noncardiac death, according to previous study.[14] The cardiac death was further subcategorized into death from ventricular tachyarrhythmia, HF death, and sudden cardiac death. Noncardiac death also was further subcategorized (malignancy, infection including sepsis and pneumonia, COPD, and aorta dissection). In 5 patients (6%), cause of death was classified as unknown.

2.5 | Endpoints

The endpoints were defined as follows: (1) A major adverse cardiac event (MACE) was defined as combined all-cause mortality and/or hospitalization due to worsening of HF; (2) all-cause mortality; (3) cardiac death; and (4) appropriate ICD therapy.

2.6 | Statistical analysis

Statistical analysis was performed using SPSS statistical software version 20.0 (IBM Corp., Armonk, New York). Continuous variables are expressed as mean ± SD and significance of differences between the 3 groups were calculated using the nonparametric Kruskal-Wallis test. Categorical variables are presented as number and percentages, and

significance of differences between groups were calculated using the χ^2 test or the Fisher exact test as appropriate. For paired categorical data the McNemar test was used. Logistic regression analysis was performed to identify predictors of super-response as one group vs nonresponse or response as the other group. Cox regression was used to analyze predictors of time until long-term clinical outcome (hospitalization due to HF and/or death). The following variables were entered as predictors into the multivariable logistic and Cox regression analysis: age, sex, LVEF, QRS width, New York Heart Association (NYHA) class at baseline, atrial fibrillation, percentage of biventricular pacing, and ischemic/nonischemic cardiomyopathy. The pool of variables considered consisted of those found to be significant at a *P* value <0.10 in univariable analysis. In a stepwise backward regression procedure, predictors with a *P* value >0.05 were removed from the model and then the model was refit. Kaplan-Meier estimates for HF hospitalization or all-cause death as well as cardiac death or appropriate ICD shock or ATP therapy across LVEF response categories were determined and statistically evaluated with the log-rank test. All *P* values reported are 2-sided, with a significance level of $P < 0.05$.

3 | RESULTS

3.1 | Overall population characteristics

Initially, 433 patients with prophylactic CRT-D indication were registered in our hospital database. In 86 patients, paired echocardiographic evaluations during baseline and follow-up were not available. Therefore, the study population consisted of 347 patients. General characteristics of study population according to the echocardiographic response are summarized in Table 1. A total of 56 (16%) patients were classified as super-responders. Female sex (odds ratio [OR]: 4.13, 95% confidence interval [CI]: 2.28-7.48), nonischemic etiology (OR: 3.14, 95% CI: 1.68-5.86), higher LVEF at baseline (OR: 1.06, 95% CI: 1.02-1.11), and wider QRS duration (OR: 1.16, 95% CI: 1.05-1.29) were associated with super-response to CRT. Also after multivariable analysis, female sex (OR: 3.06, 95% CI: 1.54-6.05), nonischemic etiology (OR: 2.70 95% CI: 1.29-5.68), higher LVEF at baseline (OR: 1.07, 95% CI: 1.02-1.13), and wider QRS duration (OR: 1.17, 95% CI: 1.04-1.32) were independently associated with super-response to CRT.

3.2 | Long-term outcome

Patients were followed for a median of 5.3 years (IQR, 4.5–6.5 years). During this period, 80 (23%) patients died (all-cause mortality). In 75 (94%) patients the mode of death was obtained. The mode of death was in 48 cases (14)% cardiac death, in 27 cases (8%) noncardiac death, and in 5 cases (1%) unknown. During total follow-up, 22% of patients were admitted to hospital due to worsening of HF. In total, MACE occurred in 33% and all-cause mortality in 23% of the entire population (Table 2). During follow-up, in 13% of patients appropriate CRT-D intervention (ATP or ICD shock) and in 12% of patients inappropriate CRT-D intervention occurred. Patients with MACE were significantly older, had more atrial fibrillation, less wide QRS duration, and more ischemic etiology compared with patients without MACE. Furthermore, in patients with MACE, NYHA class during follow-up was significantly higher, appropriate ICD therapy was higher, and percentage of biventricular pacing was lower compared with patients without MACE (Table 3).

TABLE 1 General characteristics of study population by responder category

	All Patients, N = 347	Nonresponder (LVEF <30%), n = 138	Responder (LVEF 30%–50%), n = 153	Super-responder (LVEF >50%), n = 56	*P* Value
Age, y	67 ± 9	67 ± 9	66 ± 9	66 ± 8	0.453
Female sex	30	20	28	57	<0.001
Baseline LVEF, %	24.8 ± 6.9	22.2 ± 6.0	26.2 ± 6.8	27.1 ± 7.5	<0.001
Sinus rhythm	75	77	72	78	0.543
QRS duration, ms	154 ± 30	154 ± 28	150 ± 30	165 ± 32	0.009
LBBB	83	78	84	92	0.086
RBBB	6	10	5	2	0.081
IVCD	11	12	12	6	0.498
NYHA class	2.5 ± 0.6	2.5 ± 0.6	2.4 ± 0.7	2.5 ± 0.6	0.194
Nonischemic etiology	49	34	54	61	<0.001
Medications					
Diuretics	80	85	75	82	0.112
β-Blocker	81	77	81	91	0.072
ARBs	48	47	48	52	0.839
ACEIs	77	78	74	82	0.404
Spironolactone	42	42	42	41	0.992

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; IVCD, intraventricular conduction delay; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; RBBB, right bundle branch block; SD, standard deviation.

Data are presented as % or mean ± SD.

TABLE 2 Clinical and echocardiographic outcome of 347 patients by responder category

	All Patients, N = 347	Nonresponders	Responders	Super-responders	*P* Value
Clinical follow-up duration, y	5.3 (4.5–6.5)	5.1 (4.1–6.3)	5.3 (4.6–6.7)	5.7 (4.6–6.9)	0.05
NYHA follow-up	2.0 ± 0.8	2.1 ± 0.7	1.9 ± 0.8	1.8 ± 0.7	0.07
LVEF follow-up	36.9 ± 12.3	24.4 ± 6.2	41.5 ± 4.3	54.9 ± 6.0	<0.001
Appropriate therapy, ATP and/or shock	13	21	10	0	<0.001
ATP successful	5	6	7	0	0.15
Appropriate ICD shock	10	19	7	0	<0.001
Inappropriate ICD shock	12	12	12	13	0.98
Percentage of Biv-pacing	94 ± 13	93 ± 15	94 ± 10	95 ± 15	0.02
All-cause mortality	23	37	14	13	<0.001
HF hospitalization	22	36	14	9	<0.001
MACE, all-cause mortality, and/or HF hospitalization	33	51	22	18	<0.001
Cardiac death	14	25	9	0	<0.001
Noncardiac and unknown cause of death	9	12	5	13	0.26

Abbreviations: ATP, anti-tachycardia pacing; Biv, biventricular; HF, heart failure; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; LVEF, left ventricular ejection fraction; MACE, major adverse cardiac events; NYHA, New York Heart Association; SD, standard deviation.

Data are presented as %, mean ± SD, or median (IQR).

3.3 | Super-responders and long-term outcome

In figures 1 and 2, the (reverse) Kaplan-Meier survival curves of the clinical endpoints by LVEF response categories are depicted. Super response is associated with a lower probability of adverse clinical outcomes ($P < 0.001$). The cumulative incidence of all-cause mortality in super-responders was significantly lower compared with responders and nonresponders (13% vs 9% vs 25%; $P < 0.001$). In addition, the cumulative incidence of MACE was significantly lower in super-responders compared with the other groups (18% vs 22% vs 51%; $P < 0.001$). Moreover, single components of MACE were consequently lowest in the super-responder group. The cumulative incidence of appropriate CRT-D intervention was 0% vs 10% vs 21% ($P < 0.001$). Cardiac death rate was 0% vs 8% vs 38% ($P < 0.001$). The rate of noncardiac death or unknown cause of death was not significantly different between the 3 groups (9% vs 7% vs 13%; $P = 0.43$). Inappropriate CRT-D intervention was not significantly different between the 3 groups ($P = 0.98$). Remarkably, in super-responders, the rate of inappropriate CRT-D intervention was higher than the rate of appropriate intervention (13% vs 0%; $P = 0.013$; Table 2). In total, 12 (13%) patients in the super-responder group experienced inappropriate CRT-D intervention caused by atrial fibrillation in 7 patients, lead malfunctioning in 4 patients, and T-wave oversensing in 1 patient.

3.4 | Multivariable analyses

MACE was independently associated with super-response to CRT, percentage of biventricular pacing, and age. All-cause mortality was independently associated with super-response to CRT, NYHA class at baseline, and age. Cardiac death, in univariable analysis, was associated with age, ischemic etiology, percentage of biventricular pacing, and super-response to CRT. Multivariable analysis for cardiac death and appropriate ICD therapy could not be estimated because none of the super-responders died from cardiac causes or experienced appropriate ICD therapy. Super-responders had at follow-up an independent decreased risk of MACE (hazard ratio: 0.37, 95% CI: 0.19-0.73) and all-cause mortality (hazard ratio: 0.44, 95% CI: 0.20-0.95; see Supporting Information, Table, in the online version of this article).

4 | DISCUSSION

We demonstrated in a large registry that also after long-term follow-up, super-responders to CRT had a much better prognosis than did either responders or nonresponders. Annual cardiac death rate and appropriate CRT-D intervention in super-responders was even zero. Because the annual rate of inappropriate intervention in super-responders was high, downgrading CRT-D to CRT-P in super-responders can be a matter of debate, although only randomized trials can definitely demonstrate whether this can be performed safely.

4.1 | Improvement of LVEF after CRT

The degree of response to CRT is variable because of different definitions of improvement or normalization of LVEF. Reduced LVEF is associated with risk of ventricular arrhythmia and sudden death. Randomized controlled trials and guidelines for prophylactic defibrillator implantation have relied heavily on this LVEF measurement to qualify for device candidacy.[10] Given the clinical reliance on LVEF as an indication for therapy and for assessing response to CRT-D therapy, we justified the classification of responsiveness to CRT-D on the extent of improvement in LVEF among our study patients. In our study, super-responders had a mean LVEF of 54.9% ± 6.0%.

A previous study showed that the maximal amount of functional and LV remodeling improvement was reached at 2 years following CRT and that these improvements were sustained in 5 years of follow-up.[3] In the current study, we performed echocardiographic follow-up at a median 2.8 years (IQR, 1.4–3.9 years), which means

TABLE 3 Characteristics of study population according to MACE (all-cause mortality and/or HF hospitalization)

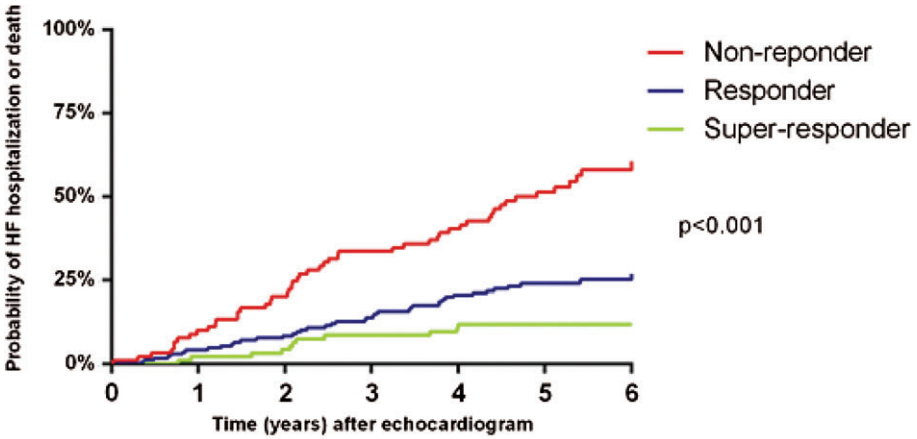
	All patients, N = 347	Without MACE, N = 233	With MACE, N = 114	*P* Value
Age, y	67 ± 9	66 ± 9	69 ± 8	0.001
Female sex	30	32	25	0.144
Baseline LVEF, %	24.8 ± 6.9	25.0 ± 7.0	24.2 ± 6.8	0.271
Sinus rhythm	75	79	68	0.036
QRS duration, ms	154.5 ± 30.3	156.8 ± 30.8	149.6 ± 28.7	0.026
LBBB	83	84	81	0.515
RBBB	6	5	9	0.301
IVCD	11	11	11	0.981
Baseline NYHA class	2.5 ± 0.6	2.4 ± 0.6	2.5 ± 0.6	0.083
Nonischemic etiology	49	54	37	0.002
Medications				
Diuretics	80	79	83	0.293
β-Blocker	81	83	77	0.209
ARBs	48	45	56	0.044
ACEIs	77	76	78	0.728
Spironolactone	42	41	43	0.752
NYHA class follow-up	2.0 ± 0.8	1.8 ± 0.7	2.5 ± 0.7	<0.001
Appropriate therapy (ATP and/or shock)	13	8	23	<0.001
Inappropriate ICD shock	12	11	15	0.262
Percentage of Biv-pacing	94 ± 13	96 ± 10	91 ± 17	0.001
Super-response to CRT	16	20	9	<0.001
Response to CRT	44	51	30	<0.001
Nonresponse to CRT	40	29	61	<0.001

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ATP, anti-tachycardia pacing; Biv, biventricular; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator; HF, heart failure; IQR, interquartile range; IVCD, intraventricular conduction delay; LBBB, left bundle branch block; MACE, major adverse cardiac events; NYHA, New York Heart Association; RBBB, right bundle branch block; SD, standard deviation.

Data are presented as % or mean ± SD.

that all potential LV remodeling has taken place. The definition for super-response to CRT varies between studies.[7–11] In this study, we defined super-response as LVEF ≥50%. Some studies used an absolute LVEF ≥35% or LVEF ≥50%, whereas others used the top quartile of LVEF changes as the definition for super-response.[6–11] Using these definitions, super response was observed in 24% to 30% of patients.[7,11]

In the current study, we demonstrated that among several baseline characteristics, female sex, nonischemic cardiomyopathy, higher LVEF at baseline, and wider QRS duration were predictors of super-response to CRT. However, previous studies reported more predictors for super-response to CRT. Female sex, nonischemic cardiomyopathy, wide QRS ≥150 ms, left bundle branch block, body mass index, QRS shortening after CRT, and smaller baseline left atrial



Patients at risk

non responders	89	80	71	59	53	34	17
responders	165	158	151	142	131	91	43
super responders	92	90	88	84	82	62	35

FIGURE 1 All-cause mortality and/or HF hospitalization by response category. Abbreviations: HF, heart failure.

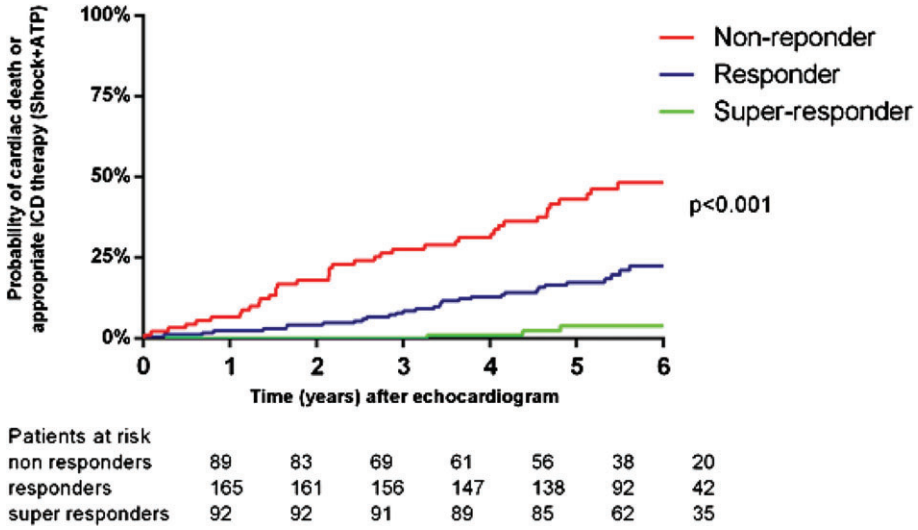


FIGURE 2 Cardiac death or appropriate ICD therapy by response category. Abbreviations: ATP, anti-tachycardia pacing; ICD, implantable cardioverter-defibrillator.

volume index were among the predictors for super-responders.[6–18] This difference may be due to slightly different study populations. Our study is smaller and our population was older (mean age, 67 years) and had more severe HF symptoms compared with patients in the Multicenter Automatic Defibrillator Implantation With Cardiac Resynchronization Therapy (MADIT-CRT) trial, which included younger (mean age, 63 years) patients with less severe HF symptoms.

4.2 | Long-term outcome in super-responders to CRT

We observed an excellent long-term prognosis without cardiac death or appropriate ICD intervention in super-responders. The all-cause mortality was 13%. One recent study[9] with 330 patients and mean follow-up of 4.1 years showed a cardiovascular death rate of 4% in patients with LVEF overcrossing 35% by CRT. In MADIT-CRT,[6] all-cause death occurred in 1.6% and all-cause death or appropriate CRT-D therapy in 5.2% of super-responders. However, in MADIT-CRT, follow-up was shorter. Another recent study comparable with our study showed a cardiovascular mortality of 1.5% and all-cause mortality of 6% in super-responders (defined as LVEF >50%).[8] One of the largest trials[12] with the same definition as our study compared the long-term survival in super-responders with an age- and sex-matched sample from the general population. All-cause mortality in super-responders at mean follow-up (5.7 ± 2.4 years) was 16%, and 4.4% received appropriate shocks for VT or VF. The annualized all-cause mortality rate for the super-responders was 3.3% and was not significantly different from the calculated survival of the age- and sex-matched sample from the general population. However, the investigator did not report the rate of cardiac death. The CRT-D device prevents specifically cardiac death and not all-cause mortality. Therefore, the findings of our study with no cardiac death in super-responders are more important and provide more insight into the death mode of super-responders.

4.3 | ICD therapy in super-responders to CRT

Reverse remodeling is associated with risk reduction for ventricular arrhythmia.[19,20] CRT partially restores dyssynchronous LV contraction and regional heterogeneity of action potential duration which may reduce ventricular arrhythmias.[21] In the current study, no appropriate ICD intervention occurred in super-responders. One previous study reported an appropriate ICD intervention rate of 7% at 5.6 years in super-responders.[8] In MADIT-CRT, the secondary endpoint of all-cause death or ICD therapy was 5.2% at 2 years. Another study[9] did not observed appropriate ICD intervention in "functional responders" to CRT at 3 years of follow-up; this follow-up is relatively short compared with that of our study. One of the recent trials[21] reported appropriate ICD therapy in 27% of super-responders compared with 34% in nonresponders during 5-year follow-up. The authors concluded that after the first year of implantation, there was no association between the extent of CRT response and reduction of appropriate device therapy. Furthermore, LVEF >45% or <45% did not predict ICD therapy after first year of implantation. It is remarkable that LVEF >45% at follow-up did not predict the ICD therapy. There are some differences between this study[21] and our study. In our study, we defined the super-response as LVEF ≥50%, whereas they defined super-response as decreased left ventricular end-systolic volume ≥30%. Another difference is that the echocardiographic follow-up occurred at 6 months after implantation, whereas we performed it at a median of 2.8 years, which means that all potential LV remodeling has taken place. Device therapy zone is also different, which could lead to more therapy. In our study, the risk of significant ventricular tachyarrhythmia in super-responders was entirely eliminated by almost normalization of LVEF as a result of CRT. The most recent meta-analysis[22] showed that recovery of LVEF post-CRT is associated with significantly reduced appropriate ICD therapy. Patients with recovery of LVEF to ≥45% and those with a primary prevention indication for ICD with LVEF recovery appear to be at lowest risk. The findings of this meta-analysis are entirely in line with our results.

4.4 | Clinical implications

Our data showed an excellent prognosis of super-responders regarding cardiac death or appropriate ICD intervention. Given the risks and discomfort portended by inappropriate shocks, we suggest that the

decision of downgrading CRT-D to CRT-P at the time of elective replacement indication or shock-lead problems should be discussed very carefully with every single patient. Moreover, based on our findings, conducting a randomized trial in super-responders, when elective replacement indication is reached, comparing continued CRT-D with downgrading to CRT-P should be encouraged.

4.5 | Study limitations

Both the large size of the study population and the long-term clinical and echocardiographic follow-up are probably the major strengths of the current study. There are also several limitations of this study. It concerns observations of a single center, one with high experience with CRT. Furthermore, although the registry was prospective, the current analysis was retrospective. We also did not evaluate other echocardiographic parameters besides LVEF. Some of the echocardiographic findings such as mitral regurgitation, diastolic function, and right ventricular function may influence the improvement of LVEF and clinical outcomes of patients. One of the limitations is that our echocardiographic follow-up was performed at a median of 2.8 years from implantation, when the majority of studies reported at 6 to 12 months after implantation. Our study focused on patients with available baseline and follow-up echocardiograms. A proportion of patients (20%) were excluded from the analysis; these patients included those who died before follow-up echocardiography or who were lost to follow-up because of referral to their own regional hospital. This proportion of 20% is, however, lower compared with the MADIT-CRT trial, which excluded 31% of patients.[6] Suboptimal LV lead placement or unfavorable pacemaker settings may, at least in part, have contributed to diminished improvement of LVEF and poorer outcome after CRT. In our population, no information is available on device programming and optimization during follow-up.

5 | CONCLUSION

Super-responders to CRT have an excellent prognosis during a median follow-up of 6 years. Female sex, nonischemic etiology, higher LVEF at baseline, and wider QRS duration are predictors of super-response.

5.1 | Conflict of interests

The authors declare no potential conflict of interests.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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